Brief Summary of the Circulatory System Devices Panel Meeting – May 6, 2014

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on May 6, 2014, to discuss, make recommendations, and vote on information related to the premarket approval application for the RESQCPR System sponsored by Advanced Circulatory Systems, Inc. The RESQCPR System is comprised of two devices: the RESQPOD 16.0 Impedance Threshold Device, and the RESQPUMP Active Compression Decompression CPR Device. These devices are used together during manual cardiopulmonary resuscitation (CPR) in an attempt to enhance venous return to the heart and blood flow to vital organs during CPR to ultimately increase survival and neurologic outcome in patients suffering from out of hospital cardiac arrest.

The sponsor has proposed the following Indications for Use:

The ResQCPR™ System is intended for use in the performance of CPR to improve the likelihood of survival with favorable neurologic function in adult patients with non-traumatic cardiac arrest.

Panel Deliberations/FDA Questions:

Important items discussed during deliberation:

- *Statistical problems*
- *Disparity with the ROC PRIMED study*
- *Potential confounding of device effectiveness by presence or absence of in-hospital therapeutic hypothermia*
- *Difficulty surrounding about how to accurately evaluate effectiveness from the device, given trial issues*
- *The device most likely improves hemodynamics, but does that translate to effectiveness – e.g., As-treated Method 3 p=0.339*
- *There appears to be a positive effectiveness signal with little/no risk.*
- *Data is equivocal statistically.*
- *Device approval may change the paradigm of how CPR is performed – i.e., standard of care may be redefined. Does effectiveness inference support this shift?*
- *Should this device be held to the same high standards for a PMA, or do we discuss "reasonable degree of effectiveness" for this patient population*

FDA Questions

1. **Study Design** – concern level over the following:

1a Contribution of the individual components was unable to be assessed:

- The panel sees this as a trial of 2 devices used together and the change in the trial arm does not cause concern as far as the interpretation of the results.

1b Preservation of alpha (α):

- The panel is expressing concern regarding the lack of the preservation of alpha.

1c Sponsor unblinding

- Panel had major concern about trial conduct and thus the interpretability of the data

1d Endpoint evaluation (mRS) made well outside window and in the absence of structured, in-person patient interviews:

- Panel agreed that since the modified Rankin score is part of the endpoint there is concern as to how it was assessed and changed for some patients.

1e Exclusion of drug overdose and metabolic patients

- Panel expressed significant concern over the removal of this group from the primary mITT analysis. Furthermore, the panel notes that if this group is included in the analysis they seem to benefit from not using the device.

1f EMS personnel were not blinded to the CPR method

- Modest concern regarding the fact that EMS personnel are not blinded, since public speakers suggested the possibility of bias in how CPR was performed. However, it would have been impossible to blind the rescuers with this trial design.

2. Evaluation of Safety

- Panel believes that the ResQCPR System appears to be safe. Pulmonary edema seems to be easily treated and did not result in poor clinical outcomes. There is some concern regarding the safety of the device in the subgroup of patients in the drug overdose subgroup of patients, in that overdose patients had worse outcomes when treated with the device.

3. Evaluation of Effectiveness

3a Overall device effectiveness:

- Concern about effectiveness – due to the issues raised in question 1 (specifically, regarding unblinding and accuracy of endpoint results) it is difficult to assess effectiveness of the device.

- Use or no use of Therapeutic hypothermia may have driven and/or significantly impacted the results (i.e., confounded any device effects).

- General concern raised –there appears to be some acknowledgement of an effectiveness signal regardless of the p-values. But the panel cannot agree that device effectiveness indeed had been demonstrated by the data presented.

3b Is there concern regarding long-term or chronic neuro impairment in the test arm vs control:

- Not concerned about neurological impairment of those saved. mRS scores among survivors appear balanced between groups.

4. Benefit Risk Profile

- Consensus of concern about effectiveness; generally seen as safe but concern about use in patients with drug overdose, and thus the benefit for the general population is somewhat unclear.
- Concerns raised over how approval might change the standard of care for CPR, particularly if effectiveness has not been appropriately documented prior to approval.
- Consideration was given to whether more effectiveness data could be collected from a registry after approval, or from another prospective study

5. Device Labeling – specifically, the indications for use statement;

- Concern regarding the need for more restrictive wording especially with respect to effectiveness – include appropriate data.
- Consider the use of the word intended vs. indicated
- Restrictions regarding etiology are most likely impractical.
- Should include comment about out of hospital use to align with how device was studied

6. Post-Approval Study (PAS)

- Overall the concept of PAS is reasonable as put forward by sponsor but should be made more robust to include items like evaluation of training and evaluation of neurological outcomes.

Vote:

The panel voted on the safety, effectiveness, and risk benefit ratio of the Advanced Circulatory Systems Inc. ResQCPR System

On Question 1, the panel voted 10/0 that the data show reasonable assurance that the ACSI ResQCPR System is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the panel voted 2/8 that there is reasonable assurance that the ACSI ResQCPR System is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the panel voted 7/3 that the benefits of the ACSI ResQCPR System do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

Although the panel chair only officially votes in the case of a tied vote, the panel chair exercised his right to express how he would have voted. His vote (unofficial) would have been yes for question 1 (reasonable assurance of safety); no for question 2 (reasonable assurance of effectiveness); and no regarding whether the benefits outweighs the risks (question 3).

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